A study of Heck cyclization reactions to form phenanthridine ring systems

Cite as:
Donaldson, L. R., Haigh, D., & Hulme, A. N. (2008). A study of Heck cyclization reactions to form phenanthridine ring systems. *Tetrahedron*, 64, 4468-4477.

Manuscript received: 23/11/2007; Accepted: 14/02/2008; Article published: 18/02/2008

A study of Heck cyclization reactions to form phenanthridine ring systems**

Lauren R. Donaldson,[1] David Haigh[2] and Alison N. Hulme[1,]*

[1]EaStCHEM, School of Chemistry, Joseph Black Building, University of Edinburgh, West Mains Road, Edinburgh, EH9 3JJ, UK.

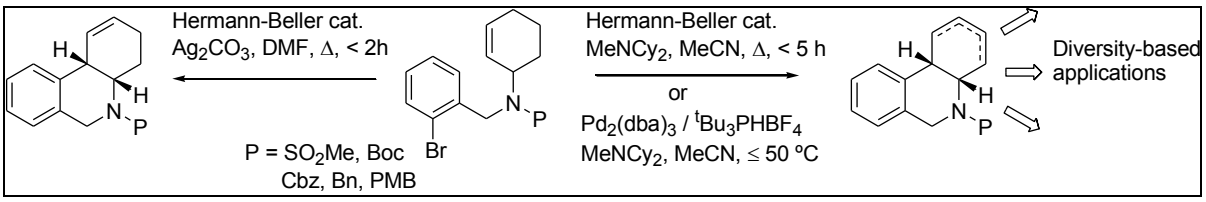
[2]GlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, UK.

[*]Corresponding author; e-mail: Alison.Hulme@ed.ac.uk, tel.: + 44 131 650 4711, fax: + 44 131 650 4743

[**]We thank the EPSRC (DTA award to LRD), GlaxoSmithKline, and the SCI (Messel Scholarship to LRD) for financial support of this work.

Supporting information:
Experimental for cyclizations in Table 2, 3 and 4. Confirmations of double bond isomers and ring junction stereochemistry. 1H and 13C Spectra for all compounds. 1H NMR integrals supporting ratios in Tables 2, 3 and 4.

Graphical abstract:



Keywords:
phenanthridines; Heck reaction; natural product scaffold

Abstract

A survey of conditions for the palladium catalyzed intramolecular Heck cyclization of protected amines has shown that the Herrmann-Beller palladacycle can be exploited under 'cationic' conditions to provide a robust and rapid route (<2 h) to the synthesis of single double-bond isomer phenanthridines in excellent yield (76-99%). In addition, the same cyclization can be performed under 'neutral' conditions to provide phenanthridines with a double-bond isomer profile suitable for exploitation in diversity-based applications. We have also shown that the highly reactive $(^{t}Bu_3P)_2Pd$ catalyst can induce cyclization at low temperatures (≤50 °C), giving similar results to the 'neutral' conditions, and offering an alternative pathway for sensitive substrates.

1. Introduction text

The phenanthridine framework **1** lies at the heart of a number of natural products including the amaryllidaceae alkaloids such as the antiviral lycorine **2**;[1,2] and the papaveraceae benzophenanthridine alkaloids such as the tubulin polymerization inhibitor chelidonine **3**[3] and isochelidonine **4** (Figure 1).[4] These, and the closely related class of phenanthridones, are known to exhibit diverse biological activities,[5] and thus present excellent targets for natural product scaffold-based libraries.[6] Whilst construction of the phenanthridone core, which lies at the heart of the antibiotic pancratistatin, has received considerable attention,[5a,b] the synthesis of phenanthridines is comparatively unstudied.

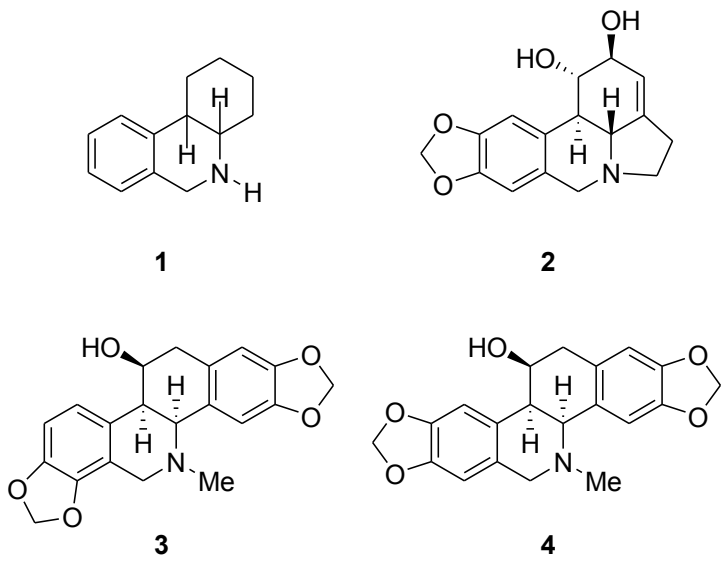


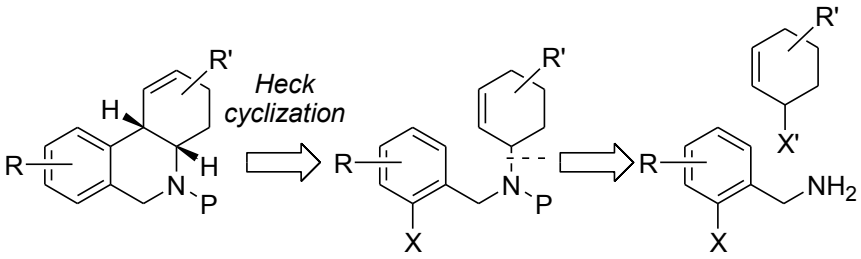
Figure 1. Phenanthridine alkaloid natural products.

We were attracted to a Heck-cyclization based approach to the phenanthridine framework as there is good precedent for *cis*-stereocontrol in formation of the 6,6-ring junction in related phenanthridone systems.[7] However, we were concerned that the conditions reported were potentially limiting in a library-based approach to the phenanthridine core due to the lengthy reaction times (typically 24-48 h) and high temperatures (typically 110-160 °C) required for the cyclization reaction. Our initial aims were thus two-fold; to develop conditions which might overcome these practical problems, whilst at the same time promoting the cyclization of a range of functionalized amine precursors to allow access to a diverse library based upon the phenanthridine core unit.

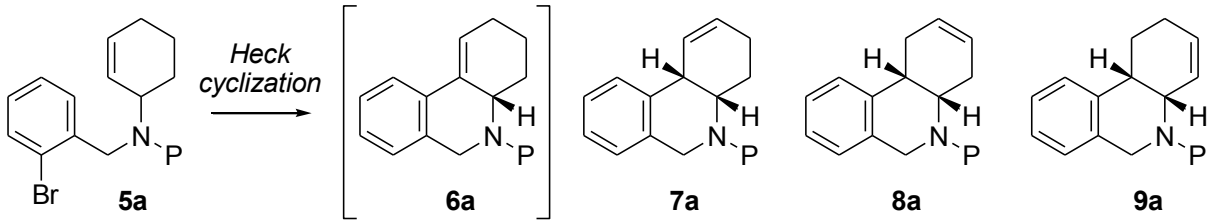
2. Results and Discussion

2.1 Catalyst screening studies

To find conditions which might be applied to the rapid synthesis of a phenanthridine library using the Heck reaction (Scheme 1), we first surveyed a range of standard catalysts. Sulfonamide **5a** (P = SO_2Me, Table 1) was found to be readily accessible through alkylation of commercially available 2-bromobenzylamine with 3-bromocyclohexene, followed by protection as the methanesulfonamide (84 % yield over 2 steps), and provided an excellent substrate for catalyst screening studies (Table 1).



Scheme 1. A Heck-cyclization based retrosynthetic analysis of a phenanthridine library.



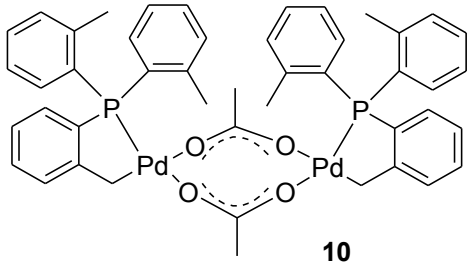
Entry	Catalyst[a]	Base	T (°C)	t (min)	Solvent	Conversion (%)[b]	Ratio **7a:8a:9a**
1	$Pd(OAc)_2/PCy_3$	$MeNCy_2$ (4 eq)	130	70	DMA	99	77:14:9
2	$Pd(OAc)_2/PCy_3$	$MeNCy_2$ (4 eq)	140	60	DMA	99	96:2:2
3	$Pd(OAc)_2/PCy_3$	$MeNCy_2$ (4 eq)	150	30	DMA	98	95:3:2
4	$Pd(OAc)_2/PCy_3$	Et_3N (4 eq)	140	70	DMA	58	90:2:8
5	$Pd(OAc)_2/PCy_3$	DIPEA (4 eq)	140	35	DMA	98	92:5:3
6	$Pd(OAc)_2/PCy_3$	K_2CO_3 (4 eq)	140	40	DMA	87	55:27:18
7	$Pd(OAc)_2/PCy_3$	2,6-lutidine (4 eq)	140	-	DMA	-	-
8	$Pd(OAc)_2/PCy_3$	$MeNCy_2$ (4 eq)	140	35	DMF	95	94:5:1
9	Herrmann-Beller (**10**)	$MeNCy_2$ (4 eq)	130	360	DMF	85	39:38:23
10	Herrmann-Beller (**10**)	$MeNCy_2$ (4 eq)	140	180	DMF	98	44:31:25
11	Herrmann-Beller (**10**)	$MeNCy_2$ (4 eq)	150	110	DMF	88	52:16:32
12	Herrmann-Beller (**10**)	AgF (1 eq)	140	180[c]	DMF	76	65:23:12
13	Herrmann-Beller (**10**)	Ag_3PO_4 (1 eq)	140	120	DMF	99	67:18:15
14	Herrmann-Beller (**10**)	Ag_2CO_3 (1 eq)	140	70	DMF	99	85:13:2

Table 1. Catalyst screening for the intramolecular Heck cyclization reaction of sulfonamide **5a** (P = SO_2Me).

Using $Pd(OAc)_2/PCy_3$ under standard conditions (Table 1, entries 1-3) the intramolecular Heck cyclization of **5a** was found to proceed to completion rapidly. In related intramolecular Heck cyclization reactions of benzamides, a range of double bond isomers have been reported, including the bridgehead $\Delta^{10b,1}$ (**6a**), $\Delta^{1,2}$ (**7a**), and $\Delta^{2,3}$ (**8a**) isomers.[8,9] In this study, none of the bridgehead double bond isomer was formed, and the *cis* $\Delta^{1,2}$ isomer (**7a**) was observed as the major product,[10] along with trace amounts of the $\Delta^{2,3}$ (**8a**) and $\Delta^{3,4}$ (**9a**) double bond isomers.[11] Investigation of a range of bases at the optimum reaction temperature (140 °C), showed DIPEA gave comparable results to those obtained in the presence of $MeNCy_2$, however Et_3N, K_2CO_3 and 2,6-lutidine gave lower conversion levels (entries 4-7). We were pleased to observe that a switch in solvent from DMA to DMF (entry 8) resulted in similar or even enhanced reactivity with almost total conversion in only 35 minutes. However, at the elevated reaction temperatures required to ensure complete conversion (140-160 °C), we encountered serious problems with reproducibility, which we ascribed to catalyst decomposition and the formation of inert palladium black.[12] The capricious nature of this catalyst system led us to investigate other possible palladium sources.

The Herrmann-Beller palladacycle (**10**, Figure 2) is well-known as a highly effective source of Pd(0) for the arylation of alkenes.[13] Its reactivity at elevated temperatures has been attributed to a slow release of Pd(0) into the reaction medium, thus maintaining a constant level of the active catalytic species throughout the

reaction.[14] Its use also has precedent in intramolecular cyclization reactions.[15] The application of **10** as a Pd(0) source in conjunction with the optimum base $MeNCy_2$ gave relatively rapid cyclization at a range of temperatures (130-150 °C), but led to a diminished selectivity for the $\Delta^{1,2}$ double bond isomer (entries 9-11). With the aim of suppressing double bond migration through a cationic reaction pathway,[16] we screened the use of a range of Ag(I) salts (entries 12-14) as additives.[17] We were pleased to discover that the use of Ag_2CO_3 in conjunction with the Herrmann-Beller catalyst led to rapid conversion (70 mins at 140 °C), good double bond isomer ratios, and excellent reproducibility.



10

Figure 2. Herrmann-Beller palladacycle

2.2 Cyclization of a range of functionalized amines

A range of functionalized amine precursors **5b-e** (Boc, Cbz, Bn, PMB) were synthesized from the same intermediate as used in formation of sulfonamide **5a** in good to excellent yields (81-90%). In all cases our optimum conditions employing the Herrmann-Beller catalyst **10** gave excellent conversions to the phenanthridine core, strongly favouring the $\Delta^{1,2}$ isomer (Table 2). With the exception of the PMB-protected amine precursor **5e**, the reactions were complete in <2 h. The Bn and PMB protected analogues in particular showed excellent selectivity for the $\Delta^{1,2}$ isomer.

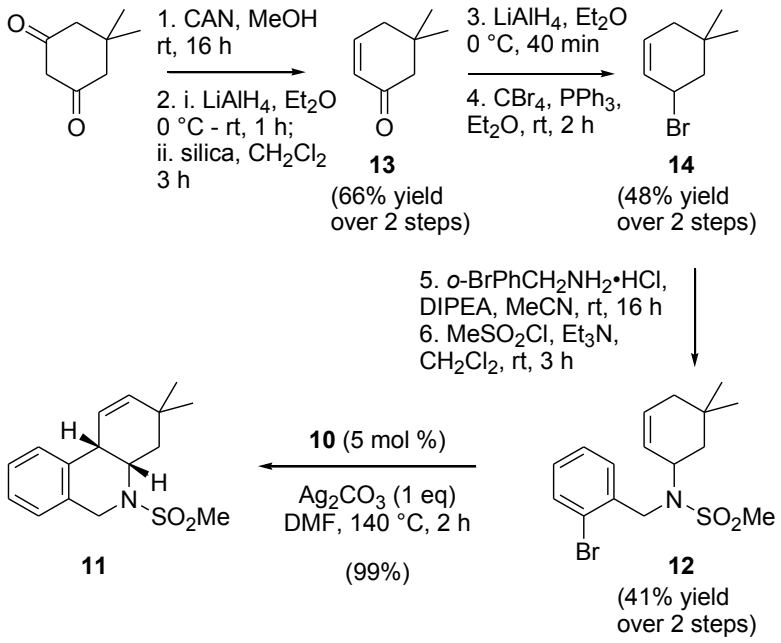
Amine	P	t (min)	Yield (%)	Ratio (7:8:9)
5a	SO_2Me	70	99	85:13:2
5b	Boc	120	99	83:15:2
5c	Cbz	120	99	92:6:2
5d	Bn	120	92	100:0:0[b]
5e	PMB	160	76	97:3:0

[a] Reagents and Conditions: aryl halide (1 eq), palladacycle **10** (5 mol %), Ag_2CO_3 (1 eq), DMF, 140 °C. [b] Minor isomer peaks could not be quantified.

Table 2. Cyclization reactions of a range of functionalized amines.[a]

The identity and ratios of the Boc and Cbz-protected products (**7b-9b** and **7c-9c** respectively) was determined by direct correlation of their ^{1}H NMR spectra with their sulfonamide counterparts (**7a-9a**); and the assignment of minor peaks was confirmed by TOCSY experiments. For the Bn and PMB products, extensive 2D NMR analysis confirmed that the major product in each of these two cases was the $\Delta^{1,2}$ isomer (**7d** and **7e** respectively), whilst the $\Delta^{2,3}$ and $\Delta^{3,4}$ minor products were assigned by analogy with their sulfonamide counterparts.

In order to assess the utility of these conditions on a substrate biased towards the formation of a single double bond isomer, we chose to synthesize the gem dimethyl analogue of the phenanthridine ring system, **11**. The sulfonamide protected cyclization precursor **12** was readily accessed (Scheme 2) through conversion of dimedone to the known enone **13**;[18,19] reduction of **13** to the corresponding enol and conversion to allylic bromide **14**;[20.21] coupling of bromide **14** with 2-bromobenzylamine; and finally sulfonamide protection of the amine (6 steps, 13 % overall yield). Heck cyclization of **12** employing the Herrmann-Beller catalyst resulted in quantitative conversion in 2 h to a colourless solid which was shown to be the desired $\Delta^{1,2}$ 3,3-dimethyl-tetrahydrophenanthridine **11**.

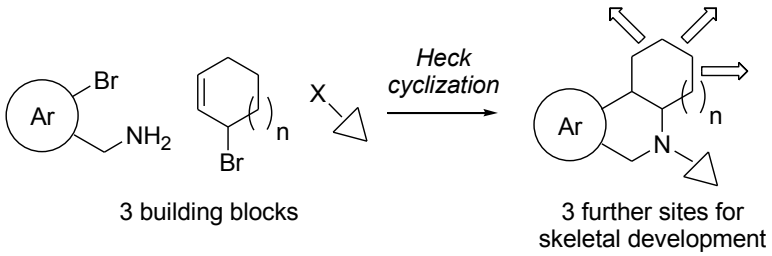


Scheme 2. Synthesis and Heck cyclization of gem dimethyl analogue **12**.

2.3 Diversity-based applications of the phenanthridine cyclization reaction

The synthesis of natural-product-like libraries based on strategies which make use of the rapid introduction of stereochemical and structural diversity,[22] is one which has gained prominence in recent years as a means to

efficiently cover chemical space.[23] The initial results obtained for the cyclization of sulfonamide **5a** under "neutral" conditions with the Hermann-Beller catalyst (Table 1, entry 10) offer considerable potential in this direction. In one step, the phenanthridine core unit is formed, whilst at the same time the potential for further diversification, through reaction of the newly-formed double bond at each of the three positions, $\Delta^{1,2}$, $\Delta^{2,3}$ and $\Delta^{3,4}$, is introduced. In combination with different amine precursors a large and diverse compound library based on the phenanthridine core might be rapidly assembled (Scheme 3).



Scheme 3. Diversity oriented synthesis of a phenanthridine library.

To determine the potential versatility of such an approach we screened the use of the Herrmann-Beller catalyst across the full range of amine precursors **5a-e** (Table 3). Whilst the Boc and Cbz protected substrates (**5b** and **5c**) behaved in a similar manner to **5a**, giving a double bond isomer profile suitable for diversity-based applications, the Bn and PMB protected substrates (**5d** and **5e**) gave predominantly the $\Delta^{1,2}$ isomer.

Amine	P	t	Yield (%)	Ratio (7:8:9)
5a	SO_2Me	3h	98	44:31:25
5b	Boc	3 h	95	36:38:26
5c	Cbz	3 h	99	33:39:28
5d	Bn	5 h	93	83:8:9
5e	PMB	5 h	93	74:13:13

[a] Reagents and Conditions: aryl halide (1 eq), $MeNCy_2$ (4 eq), palladacycle **10** (5 mol %), DMF, 140 °C.

Table 3. Cyclization under neutral Herrmann-Beller conditions.[a]

The highly reactive catalyst $(^tBu_3P)_2Pd$ has been used to conduct intermolecular Heck coupling reactions at room temperature.[24] However this catalyst system has limited precedent in intramolecular Heck cyclizations,[25] and only one example of its use at low temperatures (40 °C) has been reported,[25c] with no examples of its application in a system similar to ours. We explored the use of this catalyst with amine precursors **5a-e** (Table 4). Whilst, the intermolecular reactions are typically conducted in dioxane,[24,26-28] the use of this solvent in our system led to very low conversions. A simple solvent switch to MeCN gave much more promising results and we observed complete conversion of sulfonamide **5a** to products **7a-9a** at room temperature. However, the

Boc and Cbz protected precursors required a slightly elevated temperature (50 °C) for the cyclization reaction to proceed to completion. Intriguingly, the Bn and PMB-protected substrates **5d** and **5e** showed little or no reactivity at either temperature.

These results suggest that this low-temperature cyclization offers a viable route for the synthesis of more-sensitive members of a phenanthridine library.

Amine	P	Method	t (h)	Yield (%)	Ratio (**7**:**8**:**9**)
5a	SO_2Me	A	9	99	12:65:23
		B	4	99	55:41:4
5b	Boc	A	40	50	34:43:22
		B	7	95	34:37:29
5c	Cbz	A	40	64	53:34:13
		B	7	85	36:5:59
5d	Bn	A	72	no reaction	--
		B	40	23	n.d.[b]
5e	PMB	A	72	no reaction	--
		B	40	no reaction	--

[a] Reagents and Conditions: Method A: Aryl halide (1 eq), $Pd_2(dba)_3$ (5 mol %), $^tBu_3PHBF_4$ (10 mol %), $MeNCy_2$ (4 eq), MeCN, rt; Method B: As Method A at 50 °C. [b] not determined

Table 4. Cyclization under low temperature conditions.[a]

2.4 Preliminary mechanistic investigations

We have shown that the double bond isomer profile obtained under each of the optimized conditions shows dramatic variation, *e.g.* from 92:6:2 to 33:39:28 for cyclization of **5c**. Beller has concluded that in the intermolecular Heck reaction of arylbromides with cyclohexene and cyclopentene, double bond migration is predominantly catalyzed by the base used in the reaction, and not by a HPdX complex.[29] In this simple intermolecular equivalent of our study, the choice of solvent and base was shown to have an important influence on the extent of C-C double bond migration, whilst different catalysts showed no significant changes in selectivity. In sharp contrast, our study demonstrates that in the intramolecular Heck reaction where the two components are linked as the protected benzylamine, the palladium catalyst plays a pivotal role in double bond isomerism under otherwise identical conditions (entry 8 vs entry 10, Table 1). Furthermore, when we re-subjected the isolated $\Delta^{1,2}$ and $\Delta^{2,3}$ double bond isomers (**7a** and **8a** respectively) to each of the optimized reaction conditions, which should allow a base-catalyzed double bond migration, each isomer was recovered unchanged even after 48 h; strongly suggesting that the double bond ratios are established at the time of cyclization. Indeed when the reaction of the sulfonamide precursor **5a** was monitored by ^1H NMR, the double bond isomer ratio was found to be consistent with the final ratio from the earliest timepoint measured,

and did not show a significant deviation from this ratio through the remainder of the reaction. These results suggest that the double bond isomer ratio obtained in these intramolecular Heck cyclization reactions is a product of the differing rates of decomplexation of each catalyst compared to the rate of hydropalladation/ dehydropalladation in each case.[30]

3. Conclusions

These catalyst screening studies allow the following conclusions to be drawn: firstly, for applications of the Heck cyclization reaction to give phenanthridine ring systems where a single double bond isomer is required, the Herrmann-Beller catalyst employed under cationic conditions (Ag_2CO_3) provides a >85:15 ratio of isomers in favour of the $\Delta^{1,2}$ isomer in all cases. Excellent yields (76-99%) are obtained in short reaction times (<160 min). Where the double bond migration process is hindered (*e.g.* in the case of the gem dimethyl precursor **15**) a 99% yield of a single reaction product is obtained under these conditions. Intriguingly, for sulfonamide or carbamate protected precursors, two further options of synthetic utility have been revealed. Rapid cyclization (<5 h) to give high yields (95-99%) of an approximately equal mixture of three double bond isomers may be achieved using the Herrmann-Beller catalyst under "neutral" pathway conditions. The potential for exploitation of this result on comparatively sensitive substrates is increased by using the highly reactive ($^t Bu_3P)_2Pd$ catalyst; here cyclization may be achieved at comparatively low temperatures (r.t. – 50 °C). These results offer considerable potential for a diversity-based approach to a phenanthridine library, as in a single step both the phenanthridine core and the potential for further structural diversity are introduced. We are currently pursuing the application of this strategy to a natural product based library.

4. Experimental

4.1 General: All non-aqueous reactions were carried out under an atmosphere of nitrogen using flame- or oven-dried glassware. Unless otherwise noted, starting materials and reagents were obtained from commercial suppliers and were used without further purification. CH_2Cl_2, Et_3N and DIPEA were distilled from calcium hydride. Et_2O was dried and purified by passage through activated alumina columns using a solvent purification system from www.glasscontour.com. Anhydrous DMF and acetonitrile were used as supplied by BakerDRY. Anhydrous 1,4-dioxane was used as supplied by Aldrich. Purification by flash column chromatography was carried out using Merck Kieselgel 60 silica gel as the stationary phase. IR spectra were measured on a Biorad FTS-7 or Perkin-Elmer Paragon 1000 FT-IR spectrometer as thin films unless otherwise stated. ^1H and ^{13}C NMR spectra were measured on a Bruker AC250 or Bruker DPX360; J-values are in Hz. Melting points were determined on a Gallenkamp Electrothermal Melting Point apparatus and are uncorrected. Fast atom bombardment (FAB) mass spectra were obtained using a Kratos MS50TC mass

spectrometer at The University of Edinburgh. High performance liquid chromatography (HPLC) was carried out using a Gilson instrument fitted with a refractive index detector, using a microsorb 100-5 Si column (length 250 mm, id 21.4 mm, particle size 5 μm). A standard flow rate of 8.0 cm^3 min^{-1} was used. All solvents used for HPLC were filtered prior to use. Double bond isomer ratios were assigned on the basis of the ^1H NMR spectra which are included in the supporting information.

4.2 Preparation of protected amines 5a-e

4.2.1. N-(2-Bromo-benzyl)-cyclohex-2-enyl-amine hydrochloride

To a solution of 2-bromobenzylamine hydrochloride (6.00 g, 27.0 mmol) in MeCN (100 mL) at 0 °C was added DIPEA (18.8 mL, 108 mmol) and the reaction was stirred for 5 mins. 3-Bromocyclohexene (3.10 mL, 27.0 mmol) was added and the reaction stirred for 16 h at rt. The reaction was concentrated under reduced pressure and the residue taken up in CH_2Cl_2 (50 mL) and washed with NaCl (3 x 50 mL, sat aq.). The organics were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was taken up in CH_2Cl_2 (3 mL), HCl (30 mL, 1.0 M in Et_2O, 30.0 mmol) added and the resultant suspension filtered to afford the amine hydrochloride as a colourless solid (7.15 g, 99 %). MP 142 °C; ^1H NMR δ (250 MHz, CD_3OD) 7.79 (1H, dd, *J* 8.0, 1.3), 7.66 (1H, dd, *J* 7.6), 7.53 (1H, td, *J* 7.6, 1.3), 7.43 (1H, td, 7.9, 1.7), 6.29-6.23 (1H, m), 5.91-5.87 (1H, m), 4.46 (2H, s), 4.06-4.03 (1H, m), 2.28-2.18 (3H, m), 1.94-1.87 (3H, m); ^{13}C NMR δ (250 MHz, CD_3OD) 135.4 (CH), 133.0 (CH), 131.6 (CH), 131.1 (CH), 130.9 (C), 128.0 (CH), 124.5 (C), 120.7 (CH), 54.3 (CH), 46.9 (CH_2), 24.8 (CH_2), 23.9 (CH_2), 18.8 (CH_2); *m/z* (FAB, THIOG) 266 ($[^{81Br}M\text{-}H]^+$, 86 %), 264 ($[^{79Br}M\text{-}H]^+$, 70), 262 (27), 239 (25), 238 (28.5), 186 (91), 184 (88) ; HRMS (FAB, THIOG) Found: $[^{81Br}M\text{-}H]^+$, 266.0372. $C_{13}H_{15}N^{81}Br$ requires 266.0369. Found: $[^{79Br}M\text{-}H]^+$, 264.0383. $C_{13}H_{15}N^{79}Br$ requires 264.0388. Free Amine: R_f [3: 1 hexane: EtOAc] = 0.90; υ_{max} (CH_2Cl_2)/cm^{-1} 3361, 1466, 1436, 1010, 747; ^1H NMR δ (250 MHz, $CDCl_3$) 7.68 (1H, dd, *J* 7.9, 1.3), 7.60 (1H, dd, *J* 7.7, 1.7), 7.43 (1H, td, *J* 7.4, 1.1), 7.26 (1H, td, *J* 7.6, 1.8), 5.97-5.87 (2H, m), 4.10 (1H, d, *J* 13.8), 4.03 (1H, d, *J* 13.8), 3.38 (1H, br s), 2.17-1.66 (6H, m); ^{13}C NMR δ (62.9 MHz, $CDCl_3$) 139.5 (C), 132.5 (CH), 130.0 (CH), 129.6 (CH), 128.9 (CH), 128.2 (CH), 127.2 (CH), 123.7 (C), 52.3 (CH), 50.8 (CH_2), 29.2 (CH_2), 25.1 (CH_2), 19.9 (CH_2).

4.2.2. N-(2-Bromo-benzyl)-N-cyclohex-2-enyl-methane-sulfonamide 5a

To a solution of *N*-(2-Bromo-benzyl)-cyclohex-2-enyl-amine hydrochloride (3.90 g, 14.6 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added Et_3N (6.20 mL, 43.8 mmol) and methanesulfonyl chloride (3.40 mL, 43.8 mmol), and the reaction warmed to room temperature and stirred for 16 h. The reaction was diluted with Et_2O (30 mL) and washed with H_2O (2 x 30 mL), HCl (2 x 30 mL. 1 M aq.) and $NaHSO_3$ (2 x 30 mL, sat aq.). The organics were dried ($MgSO_4$), concentrated under reduced pressure and purified by flash chromatography (CH_2Cl_2 - 1 % MeOH in CH_2Cl_2). The resultant solid was washed with Et_2O (3 x 30 mL) and dried to afford sulfonamide protected amine **5a** as a colourless solid (4.95 g, 99 %). R_f [3: 1 hexane: EtOAc] = 0.46; MP 100 °C; υ_{max} ($CHCl_3$)/cm^{-1} 1332, 1145; ^1H NMR δ (250 MHz, $CDCl_3$) 7.67 (1H, dd, *J* 7.8, 0.8), 7.49 (1H, dd, *J*

7.9, 1.2), 7.33 (1H, td, *J* 7.7, 1.2), 7.12 (1H, m), 5.98-5.93 (1H, m), 5.53-5.47 (1H, m), 4.66-4.57 (1H, m), 4.47 (1H, dd, *J* 17.7), 4.33 (1H, d, *J* 17.7), 2.97 (3H, s), 1.99-1.92 (3H, m), 1.70-1.34 (3H, m); ^{13}C NMR δ (62.9 MHz, $CDCl_3$) 137.7 (C), 133.7 (CH), 132.1 (CH), 129.2 (CH), 128.4 (CH), 127.3 (CH), 126.5 (CH), 121.9 (C), 55.6 (CH), 47.5 (CH_2), 39.4 (CH_3), 28.7 (CH_2), 24.2 (CH_2), 21.4 (CH_2); *m/z* (FAB, THIOG) 346 ([^{81Br}M+H]$^+$, 64 %), 344 ([^{79Br}M+H]$^+$, 68), 266 (80), 264 (85); HRMS (FAB, THIOG) Found: [^{81Br}M+H]$^+$, 346.0326. $C_{14}H_{19}NO_2S^{81}Br$ requires 346.0301. Found: [^{79Br}M+H]$^+$ 344.0346. $C_{14}H_{19}NO_2S^{79}Br$ requires 344.0320.

4.2.3. (2-Bromo-benzyl)-cyclohex-2-enyl-carbamic acid *tert*-butyl ester 5b

To a suspension of *N*-(2-Bromo-benzyl)-cyclohex-2-enyl-amine hydrochloride (500 mg, 1.87 mmol) in CH_2Cl_2 (20 ml) was added Et_3N (395 µL, 2.81 mmol). After 10 mins, the reaction was cooled to 0 °C, Boc_2O (613 mg, 2.81 mmol) in CH_2Cl_2 (5 mL) added and the reaction was stirred for a further 10 mins. The reaction was warmed to room temperature and stirred for 16 h. The reaction was diluted with CH_2Cl_2 (20 mL), extracted with NaCl (3 x 20 mL, sat aq.), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (hexane: EtOAc: Et_3N, 10: 1: 0.1) afforded Boc protected amine **5b** as a colourless oil (685 mg, 90 %). R_f [3:1 hexane: EtOAc] = 0.8; MP 81 °C; υ_{max} ($CHCl_3$)/cm^{-1} 3057, 3021, 1695, 1274, 1253; ^{1}H NMR δ (360 MHz, 318 K, $CDCl_3$) 7.51 (1H, d, *J* 7.7), 7.29-7.26 (2H, m), 7.11-7.07 (1H, m), 5.83 (1H, br s), 5.50 (1H, d, *J* 10.1), 4.90 (1H, br s), 4.38 (2H, br s), 2.10-1.81 (3H, m), 1.81-1.70 (1H, m), 1.55-1.46 (2H, m), 1.35 (9H, s); ^{13}C NMR δ (90.6 MHz, 318 K, $CDCl_3$) 155.6 (C), 132.2 (CH), 131.7 (CH), 130.8 (C), 128.0 (CH), 127.7 (CH), 127.3 (CH), 126.9 (CH), 121.9 (C), 79.7 (C), 53.0 (CH), 52.6 (CH_2), 28.0 (3xCH_3), 27.3 (CH_2), 24.4 (CH_2), 21.2 (CH_2); *m/z* (FAB, THIOG) 368 ([^{81Br}M+H]$^+$, 12 %), 366 ([^{79Br}M+H]$^+$, 15), 313 (33), 312 (68), 311 (39), 310 (70), 266 (28), 232 (57), 230 (51); HRMS (FAB, THIOG) Found: [^{81Br}M+H]$^+$ 368.1046. $C_{18}H_{25}NO_2{}^{81}Br$ requires 368.1050. Found: [^{79Br}M+H]$^+$ 366.1067. $C_{18}H_{25}NO_2{}^{79}Br$ requires 366.1069.

4.2.4. (2-Bromo-benzyl)-cyclohex-2-enyl-carbamic acid benzyl ester 5c

To a suspension of NaH (143 mg, 60% dispersion in mineral oil, 3.62 mmol) in DMF (10.0 mL) at 0 °C was added *N*-(2-Bromo-benzyl)-cyclohex-2-enyl-amine hydro-chloride (500 mg, 1.65 mmol) in DMF (10.0 mL). The solution was stirred for 30 mins then benzyl chloroformate (302 µL, 2.15 mmol) was added dropwise and the reaction was warmed to room temperature and stirred for 16 h. The reaction was diluted with Et_2O (20 mL), extracted with NaCl (3 x 20.0 mL, sat aq.), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product. Flash chromatography (hexane: EtOAc: Et_3N, 100: 1: 0.1 – 100: 5: 0.1) afforded Cbz protected amine 5c as a colourless oil (570 mg, 86 %). R_f [10: 1 hexane: EtOAc] = 0.54; MP 48 °C; υ_{max} ($CHCl_3$)/cm^{-1} 3064, 3021, 1699, 1407, 1258; ^{1}H NMR δ (360 MHz, 323K, $CDCl_3$) 7.52 (1H, d, *J* 5.8), 7.40 – 7.22 (7H, m), 7.11-7.08 (1H, m), 5.87-5.85 (1H, m), 5.48 (1H, d, *J* 10.2), 5.16 (2H, br s), 4.89 (1H, br s), 4.51 (1H, d, *J* 17.4), 4.44 (1H, d, *J* 17.4), 2.11-1.84 (3H, m), 1.80-1.70 (1H, m), 1.70-1.47 (2H, m); ^{13}C NMR δ (90.6 MHz, 323K, $CDCl_3$) 156.4 (C), 138.4 (C), 136.7 (C), 132.4 (2xCH), 128.3 (CH), 127.9 (CH), 127.7 (3xCH), 127.6 (3xCH), 127.1 (CH), 122.1 (C), 67.3 (CH_2), 53.8 (CH), 47.7 (CH_2), 28.1 (CH_2), 24.5 (CH_2), 21.2 (CH_2); *m/z* (FAB, 3-NOBA) 402 ([^{81Br}M+H]$^+$, 35 %), 400 ([^{79Br}M+H]$^+$, 38), 310 (22), 308 (22), 171 (69),

169 (50) ; HRMS (FAB, THIOG) Found: $[^{81Br}M+H]^+$ 402.0821. $C_{21}H_{23}O_2{}^{81}BrN$ requires 402.0979. Found: $[^{79Br}M+H]^+$ 400.0918. $C_{21}H_{23}O_2{}^{79}BrN$ requires 400.0912.

4.2.5. Benzyl-(2-bromo-benzyl)-cyclohex-2-enyl-amine 5d

To a suspension of *N*-(2-Bromo-benzyl)-cyclohex-2-enyl-amine hydrochloride (750 mg, 2.47 mmol) in DMF (20 mL) at 0 °C, was added NaH (217 mg, 60% dispersion in mineral oil, 5.43 mmol) and the reaction stirred for 30 mins. Benzyl bromide (382 µL, 3.21 mmol) was added dropwise and the reaction warmed to room temperature and stirred for 16 h. Et_2O (20 mL) was added and the organics washed with NaCl (3 x 30 mL, sat aq.), dried ($MgSO_4$), concentrated under reduced pressure and purified by flash chromatography (hexane: EtOAc: NH_3, 100: 1: 0.1) to afford benzyl protected amine **5d** as a colourless oil (712 mg, 81 %). R_f [hexane] = 0.29; υ_{max} ($CHCl_3$)/cm^{-1} 3057, 3019, 1026; ^{1}H NMR δ (360 MHz, $CDCl_3$) 7.71 (1H, dd, *J* 7.7, 1.6), 7.49 (1H, dd, *J* 8.0, 1.2), 7.40 (2H, d, *J* 7.4), 7.31-7.27 (3H, m), 7.27-7.21 (1H, m), 7.07 (1H, td, *J* 7.9, 1.8), 5.89-5.84 (1H, m), 5.79 (1H, d, *J* 10.4), 3.81 (1H, d, *J* 15.3), 3.78 (1H, d, *J* 14.0), 3.75 (1H, d, *J* 15.3), 3.63 (1H, d, *J* 14.0), 3.39-3.36 (1H, m), 2.08-1.95 (3H, m), 1.85-1.76 (1H, m), 1.64-1.42 (2H, m); ^{13}C NMR δ (90.6 MHz, $CDCl_3$) 140.3 (C), 139.5 (C), 132.3 (CH), 130.4 (CH), 130.3 (CH), 130.2 (CH), 128.4 (2xCH), 128.0 (2xCH), 127.8 (CH), 127.2 (CH), 126.6 (CH), 124.0 (C), 55.2 (CH), 54.0 (CH_2), 53.1 (CH_2), 25.2 (CH_2), 23.5 (CH_2), 21.7 (CH_2); *m/z* (FAB, THIOG) 356 ($[^{81Br}M+H]^+$, 52 %), 354 ($[^{79Br}M+H]^+$, 47 %), 329 (35), 327 (35), 276 (75), 274 (53), 184 (34), 171 (69), 169 (71); HRMS (FAB, THIOG) Found: $[^{81Br}M+H]^+$ 356.0838. $C_{20}H_{23}NO_2{}^{81}Br$ requires 356.0838. Found: $[^{79Br}M+H]^+$ 354.0856. $C_{20}H_{23}NO_2{}^{79}Br$ requires 354.0857.

4.2.6. (2-Bromo-benzyl)-cyclohex-2-enyl-(4-methoxy-benzyl)-amine 5e

To a suspension of *N*-(2-Bromo-benzyl)-cyclohex-2-enyl-amine hydrochloride (750 mg, 2.81 mmol) in DMF (20 mL) at 0 °C was added NaH (246 mg, 60% dispersion in mineral oil, 6.18 mmol) and the reaction was stirred until homogeneous. The reaction was warmed to room temperature and stirred for 30 mins, then cooled to 0 °C, *p*-methoxybenzyl bromide (614 µL, 4.21 mmol) was added and the reaction stirred for 15 mins. The reaction was warmed to room temperature and stirred for 16 h. Et_2O (30 mL) was added, the organics washed with NaCl (3 x 20 mL, sat aq.), concentrated under reduced pressure and purified by flash chromatography (hexane: EtOAc: NH_3, 100: 1.5: 0.1) to afford PMB protected amine **5e** as a colourless oil (912 mg, 84 %). R_f [3: 1 hexane: EtOAc] = 0.81; υ_{max} ($CHCl_3$)/cm^{-1} 2857, 1541, 1508, 1457, 1248, 750; ^{1}H NMR δ (360 MHz, $CDCl_3$) 7.69 (1H, d, *J* 7.8), 7.47 (1H, dd, *J* 7.8), 7.31-7.25 (3H, m), 7.04 (1H, td, *J* 7.8, 1.7), 6.83 (2H, dd, *J* 6.7, 1.8), 5.85-5.82 (1H, m), 5.76 (1H, d, *J* 10.5), 3.76 (3H, s), 3.75 (2H, m), 3.70 (1H, d, *J* 13.8), 3.55 (1H, d, *J* 13.8), 3.34 (1H, br s), 2.04-1.93 (3H, m), 1.83-1.75 (1H, m), 1.58-1.48 (2H, m); ^{13}C NMR δ (90.6 MHz, $CDCl_3$) 158.3 (C), 139.6 (C), 132.2 (C), 132.1 (CH), 130.4 (CH), 130.1 (2xCH), 129.4 (2xCH), 127.7 (CH), 127.0 (CH), 123.9 (C), 113.4 (2xCH), 55.0 (CH_3), 54.9 (CH), 53.3 (CH_2), 52.9 (CH_2), 25.2 (CH_2), 23.4 (CH_2), 21.7 (CH_2) ; *m/z* (FAB, THIOG) 389 ($[^{81Br}M+H]^+$, 15 %), 387 ($[^{79Br}M+H]^+$, 43), 359 (53), 357 (54), 306 (43.9), 304 (41.2), 280 (21.8), 278 (24.4), 216 (35.9), 214 (21.0); HRMS (FAB, THIOG) Found: $[^{81Br}M+H]^+$ 388.1068. $C_{21}H_{25}NO^{81}Br$ requires 388.1100. Found: $[^{79Br}M+H]^+$ 386.1121. $C_{21}H_{25}NO^{79}Br$ requires 386.1120).

4.3 Heck cyclization conditions employed in Tables 2-4.

4.3.1 Conditions for Table 2

To a degassed solution of the aryl halide (1 eq) in DMF was added palladacycle **10** (5 mol %) and Ag_2CO_3 (1 eq), and the reaction was heated at 140 °C. At the conclusion of the reaction (as judged by tlc), the mixture was allowed to cool and then diluted with Et_2O (20 mL) and washed with NaCl (3 x 20 mL, sat. aq.). The organics were combined, dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography to give the stated mixture of double bond isomers.

4.3.2. Conditions for Table 3

To a degassed solution of the aryl halide (1 eq) in DMF was added palladacycle **10** (5 mol %) and $MeNCy_2$ (4 eq), and the reaction was heated at 140 °C. At the conclusion of the reaction (as judged by tlc), the mixture was allowed to cool and then diluted with Et_2O (20 mL) and washed with NaCl (3 x 20 mL, sat. aq.). The organics were combined, dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography to give the stated mixture of double bond isomers.

4.3.3. Conditions for Table 4

To a degassed solution of the aryl halide (1 eq) and $MeNCy_2$ (4 eq) in MeCN was added $Pd_2(dba)_3$ (5 mol %) and $^tBu_3PHBF_4$ (10 mol %), and the reaction stirred at room temperature (or 50 °C) for the indicated time. At the conclusion of the reaction (as judged by tlc), the mixture was diluted with Et_2O (20 mL) and washed with NaCl (3 x 20 mL, sat. aq.). The organics were combined, dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography to give the stated mixture of double bond isomers.

4.4 Data for phenanthridines 7-9

4.4.1 Sulfonamide- functionalized phenanthridines 7a-9a

(4a*SR*,10b*SR*)-5-Methanesulfonyl-3,4,4a,5,6,10b-hexa-hydro-phenanthridine 7a ($\Delta^{1,2}$ isomer). Colourless oil. R_f [3: 1 hexane: EtOAc] = 0.38; R_t [11: 9 hexane: EtOAc] 15.9 mins; ν_{max} ($CHCl_3$)/cm^{-1} 3029, 1671, 1328, 1152; ^{1}H NMR δ (360 MHz, $CDCl_3$) 7.31 (1H, d, *J* 7.5), 7.26 (1H, t, *J* 7.8), 7.19 (1H, t, *J* 7.3), 7.10 (1H, d, *J* 7.5), 5.58 (1H, ddt, *J* 10.0, 4.8, 1.9), 5.86 (1H, dtd, *J* 10.0, 3.9, 1.7), 4.59 (1H, d, *J* 16.2), 4.43 (1H, d, *J* 16.2), 4.19 (1H, dt, *J* 8.4, 5.8), 3.66 (1H, br s), 2.74 (3H, s), 2.27-2.20 (2H, m), 1.87-1.81 (2H, m); ^{13}C NMR δ (90.0 MHz, $CDCl_3$) 136.9 (C), 131.1 (C), 128.5 (CH), 127.7 (CH), 127.6 (CH), 126.7 (CH), 126.3 (CH), 125.9 (CH), 52.1 (CH), 44.1 (CH_2), 38.2 (CH_3), 37.4 (CH), 25.1 (CH_2), 24.0 (CH_2); *m/z* (FAB, THIOG) 264 ($[M+H]^+$, 19 %), 217 (25), 130 (79), 109 (38); HRMS (FAB, THIOG) Found: $[M+H]^+$ 264.1050. $C_{14}H_{18}NO_2S$ requires 264.1058. This compound was also fully characterized by COSY, HSQC and NOESY 2D NMR studies.

(4a*SR*,10b*SR*)-5-Methanesulfonyl-1,4,4a,5,6,10b-hexa-hydro-phenanthridine 8a ($\Delta^{2,3}$ isomer). Colourless solid. R_f [3: 1 hexane: EtOAc] = 0.32; R_t [11: 9 hexane: EtOAc]18.1 mins; MP 140 °C; ^{1}H NMR δ (360 MHz, $CDCl_3$) 7.29-7.23 (3H, m), 7.17 (1H, dd, *J* 6.5, 1.8), 5.69-5.66 (1H, m), 5.42 (1H, ddt, *J* 10.0, 5.1, 2.3), 4.53 (2H, s), 4.29 (1H, ddd, *J* 10.4, 4.0, 2.4), 3.26-3.22 (1H, m), 2.94 (3H, s), 2.92-2.85 (1H, m), 2.69-2.58 (1H, m), 2.28-2.23 (1H, m), 1.80-1.71 (1H, m); ^{13}C NMR δ (90.0 MHz, $CDCl_3$) 135.6 (C), 128.5 (C), 127.3 (CH), 126.5 (CH), 126.4 (CH), 125.3 (CH), 124.9 (CH), 123.8 (CH), 51.7 (CH), 45.0 (CH_2), 37.7 (CH_3), 35.8 (CH), 27.9 (CH_2), 26.5 (CH_2). This compound was also fully characterized by COSY, HSQC and NOESY 2D NMR studies.

(4a*SR*,10b*SR*)-5-Methanesulfonyl-1,2,4a,5,6,10b-hexa-hydro-phenanthridine 9a ($\Delta^{3,4}$ isomer). Colourless oil. R_f [3:1 hexane: EtOAc] = 0.39; R_t [11: 9 hexane: EtOAc] 15.4 mins; ^{1}H NMR δ (360 MHz, $CDCl_3$) 7.37 (1H, d, *J* 7.8), 7.26 (1H, t, *J* 7.2), 7.19 (1H, t, *J* 7.3), 7.07 (1H, d, *J* 7.4), 5.83-5.80 (1H, m), 5.61 (1H, dt, *J* 10.2, 1.0), 4.87-4.83 (1H, m), 4.59 (1H, d, *J* 16.5), 4.26 (1H, d, *J* 16.5), 3.39 (1H, br s), 2.83 (3H, s), 2.43-2.38 (1H, m), 2.05-1.97 (1H, m), 1.94-1.76 (2H, m); ^{13}C NMR δ (90.6 MHz, $CDCl_3$) 134.5 (C), 133.0 (CH), 132.4 (C), 127.3 (CH), 126.9 (CH), 126.1 (2xCH), 125.8 (CH), 52.4 (CH), 43.3 (CH_2), 39.8 (CH_3), 34.1 (CH), 25.3 (CH_2), 20.1 (CH_2). This compound was also fully characterized by COSY, HSQC and NOESY 2D NMR studies.

4.4.2 Boc- functionalized phenanthridines 7b-9b

(4a*SR*,10b*SR*)-4,4a,6,10b-Tetrahydro-3*H*-phenanthri-dine-5-carboxylic acid *tert*-butyl ester 7b ($\Delta^{1,2}$ isomer). R_f [10: 1 hexane: EtOAc] = 0.42; ν_{max} ($CHCl_3$)/cm^{-1} 3026, 1693, 1258, 913, 745; ^{1}H NMR δ (360 MHz, 323 K, $CDCl_3$) 7.30 (1H, d, *J* 7.5), 7.25-7.17 (2H, m), 7.12 (1H, d, *J* 7.2), 6.17-6.13 (1H, m), 5.87-5.83 (1H, m), 4.71 (1H, d, *J* 16.5), 4.41 (1H, br s), 4.39 (1H, d, *J* 16.5), 3.57 (1H, br s), 2.31-2.27 (1H, m), 2.15-2.05 (1H, m), 1.79-1.69 (1H, m), 1.61-1.40 (10H, m, 3 x CH_3+CH$_C$$H_D$); ^{13}C NMR δ (90.0 MHz, 323 K, $CDCl_3$) 155.0 (C), 137.8 (C), 132.5 (C), 128.3 (CH), 128.1 (C), 127.6 (CH), 127.3 (CH), 126.8 (CH), 126.1 (CH), 125.9 (CH), 79.6 (CH), 43.5 (CH_2), 37.3 (CH), 28.5 (3xCH_3), 25.3 (CH_2), 24.2 (CH_2); *m/z* (FAB, THIOG) 284 ([M-H]$^+$, 44 %), 228 (66), 184 (49), 130 (25); HRMS (FAB, THIOG) Found: [M-H]$^+$ 284.1643. $C_{18}H_{22}NO_2$ requires 284.1650.

Diagnostic data for 8b ($\Delta^{2,3}$ isomer). ^{1}H NMR δ (360 MHz, 323 K, $CDCl_3$) 5.73-5.65 (1H, m), 5.44-5.40 (1H, m), 4.55 (1H, d, *J* 10.9), 4.48 (1H, d, *J* 10.9), 3.21 (1H, t, *J* 4.8), 2.88 (1H, dd, *J* 29.3, 5.0), 2.67-2.55 (1H, m).

Diagnostic data for 9b ($\Delta^{3,4}$ isomer). ^{1}H NMR δ (360 MHz, 323 K, $CDCl_3$); 5.73-5.65 (1H, m), 5.53 (1H, dd, *J* 10.2, 0.9), 5.09 (1H, br s), 4.86 (1H, d, *J* 16.8), 4.25 (1H, d, *J* 16.8), 3.30 (1H, br s), 2.45-2.38 (1H, m).

4.4.3 Cbz- functionalized phenanthridines 7c-9c

(4a*SR*,10b*SR*)-4,4a,6,10b-Tetrahydro-3H-phenanthri-dine-5-carboxylic acid benzyl ester 7c ($\Delta^{1,2}$ isomer). R_f [10: 1 hexane: EtOAc] = 0.34; ν_{max} ($CHCl_3$)/cm^{-1} 3030, 1698, 1410, 1263; ^{1}H NMR δ (360 MHz, 323 K, $CDCl_3$) 7.29-7.22 (6H, m), 7.19-7.07 (2H, m), 7.01 (1H, d, *J* 6.1), 6.06-6.02 (1H, m), 5.77-5.73 (1H, m), 5.12 (2H, s), 4.72 (1H, d, *J* 16.6), 4.41 (1H, br s), 4.36 (1H, d, *J* 16.6), 3.49 (1H, br s), 2.24-2.09 (1H, m), 2.07-1.95 (1H, m), 1.67-1.63 (1H, m), 1.56-1.48 (1H, m); ^{13}C NMR δ (90.6 MHz, 323 K, $CDCl_3$) 155.5 (C), 137.6 (C), 136.9 (C), 132.0 (C), 128.4 (2xCH), 128.3 (CH), 127.9 (CH), 127.8 (2xCH), 127.6 (CH), 127.1 (CH), 127.0 (CH), 126.0 (CH), 126.0 (CH), 67.1 (CH_2), 50.7 (CH), 43.6 (CH_2), 37.2 (CH), 25.1 (CH_2), 24.2 (CH_2) ; *m/z* (FAB, THIOG) 320 ($[M+H]^+$, 24 %), 318 ($[M-H]^+$, 51), 274 (37), 228 (26), 154 (61); HRMS (FAB, THIOG) Found: $[M-H]^+$ 318.1483. $C_{21}H_{20}NO_2$ requires 318.1494.

Diagnostic data for 8c ($\Delta^{2,3}$ isomer). ^{1}H NMR δ (360 MHz, 323 K, $CDCl_3$) 5.69-5.65 (1H, m), 5.41-5.37 (1H, m), 4.65 (1H, d, *J* 16.6), 4.59 (1H, d, *J* 16.6), 3.20 (1H, br s), 2.88-2.81 (1H, m), 2.63-2.55 (1H, m).

Diagnostic data for 9c ($\Delta^{3,4}$ isomer). ^{1}H NMR δ (360 MHz, 323 K, $CDCl_3$) 5.75-5.71 (1H, m), 5.55 (1H, d, *J* 9.7), 4.95 (1H, d, *J* 16.6), 4.33 (1H, d, *J* 16.6), 3.33 (1H, br s).

4.4.4 Bn-functionalized phenanthridines 7d-9d

(4a*SR*,10b*SR*)-5-(Benzyl)-3,4,4a,5,6,10b-hexahydro-phenanthridine 7d ($\Delta^{1,2}$ isomer). R_f [10: 1 hexane: EtOAc] = 0.44; ν_{max} ($CHCl_3$)/cm^{-1} 3025, 1642, 1602, 1260; ^{1}H NMR δ (360 MHz, $CDCl_3$) 7.35 (2H, d, *J* 7.0), 7.29-7.20 (4H, m), 7.19 (1H, t, *J* 7.6), 7.10 (1H, t, *J* 7.6), 6.89 (1H, d, *J* 7.6), 6.06-6.02 (1H, ddt, *J* 9.8, 4.2, 1.8), 5.73-5.70 (1H, ddt, *J* 9.8, 5.5, 2.4), 3.89 (1H, d, *J* 13.3), 3.75 (1H, d, *J* 15.6), 3.66 (1H, d, *J* 13.3), 3.58 (1H, br s), 3.54 (1H, d, *J* 15.6), 3.14 (1H, ddd, *J* 10.6, 5.2, 2.5), 2.21-2.07 (2H, m), 1.86-1.77 (1H, m), 1.69-1.61 (1H, m); ^{13}C NMR δ (90.0 MHz, $CDCl_3$) 139.0 (C), 137.7 (C), 133.4 (C), 128.8 (CH), 128.7 (2xCH), 128.2 (2xCH), 127.7 (CH), 127.4 (CH), 126.9 (CH), 126.4 (2xCH), 125.2 (CH), 58.4 (CH_2), 56.1 (CH), 50.9 (CH_2), 37.8 (CH), 24.3 (CH_2), 19.4 (CH_2); *m/z* (FAB, THIOG) 276 ($[M+H]^+$, 76 %), 200 (35), 184 (55), 154 (93), 136 (83); HRMS (FAB, THIOG) Found: $[M+H]^+$ 276.1755. $C_{20}H_{22}N$ requires 276.1754. This compound was also fully characterized by COSY, HSQC and NOESY 2D NMR studies.

Diagnostic data for 8d ($\Delta^{2,3}$ isomer). ^{1}H NMR δ (360 MHz, $CDCl_3$) 5.70-5.67 (1H, m), 5.58-5.55 (1H, m), 2.74-2.65 (1H, m).

Diagnostic data for 9d ($\Delta^{3,4}$ isomer). ^{1}H NMR δ (360 MHz, $CDCl_3$) 5.96-5.92 (1H, m), 5.89-5.86 (1H, m).

4.4.5 PMB- functionalized phenanthridines 7e-9e

(4a*SR*,10b*SR*)-5-(4-Methoxy-benzyl)-3,4,4a,5,6,10b-hexahydro-phenanthridine 7e ($\Delta^{1,2}$ isomer). R_f [10: 1 hexane: EtOAc] = 0.23; ν_{max} ($CHCl_3$)/cm^{-1} 3024, 1647, 1609, 1511; ^{1}H NMR δ (360 MHz, $CDCl_3$) 7.33-7.29

(3H, m), 7.18 (1H, t, *J* 7.3), 7.10 (1H, t, *J* 7.6), 6.96 (1H, d, *J* 7.6), 6.90-6.88 (2H, m), 6.12-6.08 (1H, m), 5.79-5.76 (1H, m), 3.89 (1H, d, *J* 13.0), 3.82 (3H, s), 3.80 (1H, d, *J* 16.1), 3.67 (1H, d, *J* 13.0), 3.62 (1H, br s), 3.59 (1H, d, *J* 16.1), 3.12 (1H, ddd, *J* 10.6, 5.4, 2.6), 2.20-2.00 (2H, m), 1.90-1.63 (2H, m); ^{13}C NMR δ (90.0 MHz, $CDCl_3$) 158.6 (C), 137.7 (C), 133.4 (C), 130.9 (C), 129.9 (2xCH), 128.8 (CH), 127.6 (CH), 127.4 (CH), 126.4 (CH), 126.3 (CH), 125.2 (CH), 113.6 (2xCH), 57.7 (CH_2), 55.9 (CH), 55.1 (CH_3), 50.8 (CH_2), 37.8 (CH), 24.4 (CH_2), 19.2 (CH_2); *m/z* (FAB, THIOG) 306 ($[M+H]^+$, 56 %), 305 ($[M]^+$, 58), 304 ($[M-H]^+$, 69), 251 (12.4), 184 (46.1); HRMS (FAB, 3-NOBA) Found: $[M]^+$ 305.1779. $C_{21}H_{23}NO$ requires 305.1780. This compound was also fully characterized by COSY, HSQC and NOESY 2D NMR studies.

Diagnostic data for 8e ($\Delta^{2,3}$ isomer). ^{1}H NMR δ (360 MHz, $CDCl_3$) 5.68-5.65 (1H, m), 5.56-5.53 (1H, m), 3.98 (1H, d, *J* 13.2), 3.18 (1H, br s), 2.71-2.65 (1H, m).

Diagnostic data for 9e ($\Delta^{3,4}$ isomer). ^{1}H NMR δ (360 MHz, $CDCl_3$) 5.96-5.91 (1H, m), 5.90-5.84 (1H, m), 4.05 (1H, *J* 13.3), 3.11 (1H, br s).

4.5 Synthesis and cyclization of gem dimethyl analogue 12

4.5.1 5,5-Dimethyl-cyclohex-2-enol[20]

To a solution of enone **13**[19] (661 mg, 5.32 mmol) in Et_2O (12 mL) at 0 °C was added portionwise $LiAlH_4$ (201 mg, 5.32 mmol). The reaction was stirred for at 0 °C for 40 mins then quenched by the addition of $Na_2SO_4.5H_2O$ portionwise. The reaction was filtered and the filtrate vigorously stirred with potassium sodium tartate (50 mL, sat. aq.) for 1 h. The organic phase was separated and the aqueous phase washed with Et_2O (3 x 40 mL). The combined organics were dried ($MgSO_4$) and concentrated under reduced pressure to afford 5,5-dimethyl-cyclohex-2-enol as a colourless oil (525 mg, 72 %). R_f [3: 1 hexane: EtOAc] = 0.37; υ_{max} ($CHCl_3$)/cm^{-1} 3336, 2952, 1650, 1454, 1089, 1037, 725; ^{1}H NMR δ (250 MHz, $CDCl_3$) 5.71 (2H, s), 4.29-4.22 (1H, m), 1.88-1.57 (3H, m), 1.31 (1H, dd, *J* 12.3, 8.7), 1.00 (3H, s), 0.92 (3H, s);^{13}C NMR δ (62.9 MHz, $CDCl_3$) 129.1 (CH), 128.0 (CH), 66.2 (CH), 45.3 (CH_2), 38.9 (CH_2), 31.2 (CH_3), 30.7 (C), 26.0 (CH_3); *m/z* (FAB, THIOG) 149 ($[M+Na]^+$, 33 %), 127 ($[M+H]^+$, 5), 125 ($[M-H]^+$, 12), 124 (18), 111 (53); HRMS (FAB, THIOG) Found: $[M-H]^+$ 125.0968. $C_8H_{13}O$ requires 125.0966.

4.5.2 3-Bromo-5,5-dimethyl-cyclohex-2-ene 14

To a stirred solution of 5,5-dimethyl-cyclohex-2-enol (2.00 g, 15.8 mmol) and CBr_4 (11.1 g, 33.3 mmol) in Et_2O (75 mL) at 0 °C was added PPh_3 (8.00 g, 33.3 mmol). The reaction was warmed to room temperature and stirred for 2 h. The reaction was filtered and the filtrate concentrated under reduced pressure to afford a colourless solid and yellow oil. These were washed with pentane (2 x 100 mL) and the combined washings dried ($MgSO_4$) and concentrated under reduced pressure to afford bromide **14** as a pale yellow oil (2.00 g, 67 %). This material was found to be unstable to flash chromatography and thus was used without further purification. R_f [3: 1 hexane: EtOAc] = 0.46; υ_{max} ($CHCl_3$)/cm^{-1} 1437, 1120, 723, 694; ^{1}H NMR δ (250 MHz,

$CDCl_3$) 5.90-5.84 (1H, m), 5.75-5.71 (1H, m), 4.79-4.77 (1H, m), 2.14-1.88 (3H, m), 1.80-1.70 (1H, m), 1.02 (3H, s), 0.96 (3H, s);^{13}C NMR δ (62.9 MHz, $CDCl_3$) 129.0 (CH), 128.2 (CH), 47.5 (CH), 46.7 (CH_2), 38.1 (CH_2), 31.9 (C), 30.7 (CH_3), 25.4 (CH_3).

4.5.3 *N*-(2-Bromo-benzyl)-5,5-dimethylcyclohex-2-enyl-amine

To a suspension of 2-bromobenzylamine hydrochloride (412 mg, 1.85 mmol) in MeCN (20 mL) was added DIPEA (1.30 mL, 7.40 mmol) and the reaction stirred for 10 mins. Bromide **14** (700 µL, 3.70 mmol) was added dropwise and the reaction stirred at room temperature for 16 h. The reaction was concentrated under reduced pressure and the residue taken up in CH_2Cl_2 (20 mL) and washed with NaCl (3 x 20 mL, sat. aq.). The combined organics were dried ($MgSO_4$) and concentrated under reduced pressure to afford *N*-(2-bromo-benzyl)-5,5-dimethylcyclohex-2-enyl-amine as a brown oil (340 mg, 63 %). R_f [3: 1 hexane: EtOAc] = 0.37; υ_{max} ($CHCl_3$)/cm^{-1} 3307, 1776, 1651, 1466, 1025, 750; ^{1}H NMR δ (360 MHz, $CDCl_3$) 7.53 (1H, dd, *J* 7.9, 1.2), 7.46 (1H, dd, *J* 6.1, 1.6), 7.28 (1H, t, *J* 7.4, 6.1), 7.11 (1H, td, *J* 7.8, 1.6), 5.76-5.70 (2H, m), 3.92 (2H, s), 3.31-3.24 (1H, m), 1.92 (1H, dd, *J* 17.8, 3.4), 1.79-1.71 (2H, m), 1.23 (1H, t, *J* 10.6), 1.00 (3H, s), 0.92 (3H, s); ^{13}C NMR δ (90.6 MHz, $CDCl_3$) 139.6 (C), 132.5 (CH), 130.0 (CH), 128.4 (CH), 128.3 (CH), 127.3 (CH), 127.2 (CH), 123.7 (C), 52.0 (CH), 50.7 (CH_2), 43.2 (CH_2), 39.0 (CH_2), 31.8 (CH_3), 30.2 (C), 25.4 (CH_3); *m/z* (FAB, THIOG) 296 ([^{81Br}M+H]$^+$, 96 %), 294 ([^{79Br}M+H]$^+$, 100), 239 (25), 188 (33), 186 (51), 171 (42), 169 (48) ; HRMS (FAB, THIOG) Found: [^{81Br}M+H]$^+$ 296.0845. $C_{15}H_{21}N^{81}Br$ requires 296.0837. Found: [^{79Br}M+H]$^+$, 294.0848. $C_{15}H_{21}N^{79}Br$ requires 294.0857.

4.5.4 *N*-(2-Bromo-benzyl)-*N*-5,5-dimethylcyclohex-2-enyl-methanesulfonamide 12

To *N*-(2-bromo-benzyl)-5,5-dimethylcyclohex-2-enyl-amine (180 µL, 0.62mmol) in CH_2Cl_2 (5 mL) at 0 °C was added Et_3N (262 µL, 1.87 mmol) and methanesulfonyl chloride (214 µL, 1.87 mmol). The reaction was warmed to room temperature and stirred for 3 h. The reaction was extracted with HCl (2 x 10 mL, 1 M aq.) then NaOH (2 x 10 mL, 1 M aq.) and the combined organics dried ($MgSO_4$), concentrated under reduced pressure and purified by flash chromatography (hexane: EtOAc, 10: 1 – 5: 1) to afford sulfonamide **12** as a colourless oil (150 mg, 65 %). R_f [3: 1 hexane: EtOAc] = 0.77; υ_{max} ($CHCl_3$)/cm^{-1} 1335, 1159, 913, 745; ^{1}H NMR δ (360 MHz, $CDCl_3$) 7.66 (1H, d, *J* 7.0), 7.50 (1H, dd, *J* 8.0, 1.2), 7.32 (1H, td, *J* 7.6, 0.7), 7.11 (1H, *J* 7.6, 1.8), 5.89-5.83 (1H, dddd, *J* 10.3, 5.2, 2.7, 2.5), 5.49 (1H, dd, *J* 10.3, 1.3), 4.63-4.47 (1H, m), 4.45 (1H, d, *J* 17.6), 4.31 (1H, d, *J* 17.6), 2.98 (3H, s), 1.92-1.83 (1H, m), 1.75-1.68 (1H, m), 1.68-1.60 (1H, m), 1.30-1.25 (1H, m), 0.95 (3H, s), 0.91 (3H, s) ; ^{13}C NMR δ (90.6 MHz, $CDCl_3$) 137.7 (C), 132.1 (2xCH), 129.3 (CH), 128.5 (CH), 127.4 (CH), 125.1 (CH), 122.0 (C), 54.9 (CH), 47.7 (CH_2), 40.8 (CH_2), 39.5 (CH_3), 38.2 (CH_2), 31.7 (CH_3), 31.0 (C), 24.8 (CH_3); *m/z* (FAB, THIOG) 374 ([^{81Br}M+H]$^+$, 80 %), 372 ([^{79Br}M+H]$^+$, 93), 294 (49), 292 (53), 264 (23), 262 (12), 171 (100), 169 (100); HRMS (FAB, THIOG) Found: [^{81Br}M+H]$^+$, 374.0612. $C_{16}H_{23}O_2NS^{81}Br$ requires 374.0612. Found: [^{79Br}M+H]$^+$, 372.0628. $C_{16}H_{23}O_2NS^{79}Br$ requires 372.0633.

4.5.5 (4a*SR*,10b*SR*)-3,3-Dimethyl-5-Methanesulfonyl-4,4a,5,6,10b-tetrahydro-phenanthridine 11.

The general procedure for Table 2 was employed using sulfonamide **12** (40 mg, 0.11 mmol), palladacycle 10 (5.0 mg, 5.4 μmol) and Ag_2CO_3 (30 mg, 0.11 mmol) in DMF (3 mL). After 2 h at 140 °C, work up and column chromatography (10:1 – 5:1, hexane:EtOAc) afforded phenanthridine **11** as a colourless solid (31 mg, 99 %). R_f [3: 1 hexane: EtOAc] = 0.48; MP 104 °C; ν_{max} ($CHCl_3$)/cm^{-1} 2957, 1332, 1153; ^{1}H NMR δ (360 MHz, $CDCl_3$) 7.32 (1H, d, *J* 7.5), 7.24 (1H, t, *J* 7.3), 7.20 (1H, t, *J* 7.9), 7.10 (1H, d, *J* 7.3), 6.03 (1H, dd, *J* 10.0, 5.6), 5.59 (1H, d, *J* 10.0), 4.60 (1H, d, *J* 16.2), 4.43 (1H, d, *J* 16.2), 4.41 (1H, dd, *J* 15.5, 6.2), 3.59 (1H, t, *J* 5.6), 2.87 (3H, s), 1.64-1.60 (2H, m), 1.15 (3H, s), 0.94 (3H, s); ^{13}C NMR δ (90.6 MHz, $CDCl_3$) 138.7 (CH), 136.3 (C), 130.3 (C), 127.9 (CH_2), 127.3 (CH), 126.1 (CH), 126.0 (CH), 123.7 (CH), 49.8 (CH), 43.3 (CH_2), 39.0 (CH_3), 38.2 (CH_2), 36.6 (CH), 34.0 (C), 30.3 (CH_3), 28.3 (CH_3); *m/z* (FAB, THIOG) 292 ($[M+H]^+$, 100 %), 291 ($[M]^+$, 82), 213 (44), 197 (40), 165 (12), 130 (15), 94 (89); HRMS (FAB, THIOG) Found: $[M+H]^+$ 292.1371. $C_{16}H_{22}NO_2S$ requires 292.1371.

References

[1] Pettit, G. R.; Venkatswamy, G.; Herald, D. L.; Singh, S.B.; Cragg, G. M.; Schmidt, J. M.; Boettner, F. E.; Williams, M.; Sagawa, Y. *J. Nat. Prod.* **1986**, *49*, 995-1002.

[2] a) Unver, N. *Phytochem Rev.* **2007**, *6*, 125-135. b) Lewis, J. R. *Nat. Prod. Rep*. **1994**, *11*, 329-332.

[3] a) Grynkiewicz, G.; Chojecka-Koryn, E.; Gadzikowska, A.; Chodkowska, E.; Jagiello-Wojtowicz. *Eur. J. Med. Chem.* **2001**, *36*, 951-960. b) Panzer, A.; Joubert, A. M.; Bianchi, P. C.; Hamel, E.; Seegers, J. C. *Eur. J. Cell. Biol.* **2001**, *80*, 111-118. c) Probst, J. M. *Ann. Pharm.* **1839**, *29*, 113-135.

[4] De Rosa, S.; Di Vincenzo, G. *Phytochemistry* **1992**, *31*, 1085-1086.

[5] a) Jin, Z. *Nat. Prod. Rep*. **2005**, *22*, 111-126. b) Rinner, U.; Hudlicky, T. *Synlett* **2005**, *3*, 365-387. c) Kamigauchi, M.; Noda, Y.; Nishijo, J.; Iwasaki, K.; Tobetto, K.; In, Y.; Tomoo, K.; Ishida, T. *Bioorg. Med. Chem.* **2005**, *13*, 1867-1872. d) Brewster, W. K.; Nichols, D. B.; Watts, V. J.; Riggs, R. M.; Mottola, D.; Mailman, R. B. *J. Med. Chem.* **1995**, *38*, 318-327.

[6] a) Balamurugan, R.; Dekkerab F. J.; Waldmann H. *Mol. BioSyst.* **2005**, *1*, 36-45. b) Abel, U.; Koch, C.; Speitling, M.; Hansske, F. G. *Curr. Opin. Chem. Biol.* **2002**, *6*, 453-458.

[7] Grigg, R.; Sridhara, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron* **1990**, *46*, 4003-4018.

[8] a) Chida, N.; Ohtsuka, M.; Ogawa, S. *Tetrahedron Lett*. **1991**, *32*, 4525-4528. b) Grigg, R.; Loganathan, V.; Santhakumar, V.; Sridharan, V.; Teasdale, A. *Tetrahedron Lett*. **1991**, *32*, 687-690.

[9] a) Jacobi von Wangelin, A.; Neumann, H.; Goerdes, D.; Huebner, S.; Wendler, C.; Klaus, S.; Struebing, D.; Spannenberg, A.; Jiao, H.; El Firdoussi, L.; Thurow, K.; Stoll, N.; Beller, M. *Synthesis* **2005**, *12*, 2029-2038. b) Zhao, S.; Totleben, M. J.; Mizsak, S. S.; Freeman, J. P.; Szmuszkovicz, J. *Heterocycles* **2000**, *52*, 325-332.

[10] Unequivocal confirmation of the *cis* ring junction stereochemistry was gained later in this study through hydrogenation of a mixture of **7-9b**, followed by removal of the Boc group under acidic conditions (TFA, MeOH). Comparison of the ^{1}H and ^{13}C NMR data of the resultant phenanthridine with literature data allowed stereochemical assignment. [This result was in good accord with the strong nOe observed across the ring junction in all analogues.]

[11] The identity of these minor products as double bond isomers was confirmed when a mixture of **7-9a** was treated under hydrogenation conditions to give one saturated product. Each of these double bond isomers was also fully characterized by extensive COSY, HSQC and 2D NOESY NMR following separation by HPLC.

[12] Rothenberg, G.; Cruz, S. C.; van Strijdonck, G. P. F.; Hoefsloot, H. C. J. *Adv. Synth. Catal*. **2004**, *346*, 467-473.

[13] a) Dupont, J.; Consorti, C. S.; Spencer J. *Chem. Rev.* **2005**, *105*, 2527-2571. b) Beletskaya, I. P.; Cheprakov, A. V. *J. Organomet. Chem.* **2004**, *689*, 4055-4082. c) Herrmann, W. A.; Brossmer, C.; Öfele, K.; Reisinger, C.-P.; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1844-1848.

[14] Blackmond, D. G.; Schultz, T.; Mathew, J. S.; Loew, C.; Rosner, T.; Pfaltz, A. *Synlett* **2006**, *18*, 3135-3139.

[15] a) Tietze, L. F.; Kahle, K.; Raschke, T. *Chem. Eur. J*. **2002**, *8*, 401-407. b) Tietze, L. F.; Schirok, H.; Wohrmann, M.; Schrader, K. Eur. *J. Org. Chem*. **2000**, *13*, 2433-2444. c) Tietze, L. F.; Schirok, H. *J. Am. Chem. Soc.* **1999**, *121*, 10264-10269.

[16] a) Knowles, J. P.; Whiting, A. *Org. Biomol. Chem.* **2007**, *5*, 31-44. b) Crisp, G. T. *Chem. Soc. Rev*. **1998**, *27*, 427-436.

[17] Karabelas, K.; Westerlund, C.; Hallberg, A. *J. Org. Chem*. **1985**, *50*, 3896-3900.

[18] Banerjee, B.; Mandal, S. K.; Roy, S. C. *Chem. Lett*. **2006**, *35*, 16-17.

[19] Shapiro, B. L.; Johnston Jr, M. D.; Proulx, T. W. *J. Am. Chem. Soc.* **1973**, *95*, 520-526.

[20] Roberts, M. R.; Parsons, W. H.; Schlessinger, R. H. *J. Org. Chem.* **1978**, *43*, 3970-3972.

[21] García Martinez, A.; Martínez Alvarez, R.; Madueño Casado, M.; Subramanian, L. R.; Hanack, M. *Tetrahedron* **1987**, *43*, 275-279.

[22] a) Balamurugan, R.; Dekker, F. J.; Waldmann, H. *Mol. Biosyst.* **2005**, *1*, 36-45. b) Burke, M. D.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 46-58.

[23] a) Thomas, G. L.; Wyatt, E. E.; Spring, D. R. *Curr. Op. Drug. Disc. Devel.* 2006, *9*, 700-712. b) Arya, P.; Joseph, R.; Gan, Z.; Rakic, B. *Chem. Biol.* **2005**, *12*163-180.

[24] Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989-7000

[25] a) Tietze, L. F.; Stewart, S. G.; Polomska, M. E. *Eur. J. Org. Chem*. **2005**, *9*, 1752-1759. b) Cropper, E. L.; White, A. J. P.; Ford, A.; Hii, K. K. *J. Org. Chem*. **2006**, *71*, 1732-1735. c) Lautens, M.; Fang, Y. *Org. Lett*. **2003**, *5*, 3679-3682. d) Worden, S. M.; Mapitse, R.; Hayes, C. J. *Tet. Lett*. **2002**, *43*, 6011-6014.

[26] a) Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed*. **2002**, *41*, 4176-4211. b) Littke, A. F.; Fu, G. C. *J. Org. Chem*. **1999**, *64*, 10-11.

[27] a) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575-5580. b) Shaughnessy, K. H.; Kim, P.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 2123-2132.

[28] a) Lapierre, A. J. B.; Geib, S. J.; Curran, D. P. *J. Am. Chem. Soc.* **2007**, *129*, 494-495. b) Tietze, L. F.; Stewart, S. G.; Polomska, M. E. *Eur. J. Org. Chem.* **2005**, *9*, 1752-1759. c) Lautens, M.; Fang, Y.-Q. *Org. Lett*. **2003**, *5*, 3679-3682.

[29] Hartung, C. G.; Köhler, K.; Beller, M. *Org. Lett.* **1999**, *1*, 709-711.

[30] It has recently been noted that double bonds may "walk" up to 14 carbon atoms by such a mechanism: Ma, S.; Yu, Z. *Angew. Chem. Int. Ed.* **2003**, *42*, 1955-1957.